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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/302,863	04/30/1999	RAYMOND G. GOODWIN	2519	7568

22932 7590 08/08/2006

IMMUNEX CORPORATION
LAW DEPARTMENT
1201 AMGEN COURT WEST
SEATTLE, WA 98119

EXAMINER	
ROMEO, DAVID S	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 08/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/302,863	GOODWIN ET AL.	
	Examiner	Art Unit	
	David S. Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-30,32,35 and 37-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-30, 32, 35 and 37-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Ex parte prosecution is resumed.

Claims 15–30, 32, 35 and 37–40 are pending.

New Formal Matters, Objections, and/or Rejections:

Claim Rejections - 35 USC § 103

Claims 15–16, 19–21, 23–25, 27–30, 32, 35, and 37–40 rejected under 35 U.S.C. 103(a) as being unpatentable over Gross (U. S. Publication No. 20060067933) in view of Bram (WO 98/39361) and Yu (WO 98/18921).

Gross discloses that TACI (WIPO Publication WO 98/39361) binds to the TNF ligand neutrokine-α (WIPO Publication, WO 98/18921) (paragraphs [0003]-[0004]). BR43x2, TACI, and BCMA would be useful to regulate the activity of ztnf4 in particular, the activation of B cells (paragraph [0004]). The disclosure relied upon in Gross has an effective filing date of 01/07/1999 obtained via U.S. Provisional application No. 60/115,068.

TACI is identical to the present application's SEQ ID NO: 2, and neutrokine-α is identical to the present application's SEQ ID NO: 4, as indicated below, respectively:

```
Title:          >US-09-302-863-2
Description:    (1-293) from US09302863.pep
Perfect Score:  2210
Sequence:       1 MSGLGRSRRGGRSRVDQEER.....IPDSGLGIVCVPAQEGGPGA 293

Scoring table:  PAM 150
                Gap 11

Database:       a-geneseq35

                                SUMMARIES

Result          %
                Query
   No.  Score   Match Length DB  ID          Description            Pred. No.
 ------------------------------------------------------------------------------
     1   2210  100.0    293 36  W75783      Human lymphocyte surf  6.58e-223

                                ALIGNMENTS

RESULT    1
ID   W75783 standard; Protein; 293 AA.
```

```
AC   W75783;
DT   18-JAN-1999  (first entry)
DE   Human lymphocyte surface receptor TACI.
KW   TACI; transmembrane activator and CAML-interactor;
KW   calcium signal-modulating cyclophilin ligand; human;
KW   lymphocyte surface receptor; human; B-cell; B lymphocyte;
KW   infection; cancer; rheumatoid arthritis; autoimmune disease;
KW   glomerulonephritis; immunosuppressive; graft versus host disease;
KW   transplant rejection; therapy.
OS   Homo sapiens.
FH   Key             Location/Qualifiers
FT   Domain          1..166
FT                   /label= Extracellular_domain
FT                   /note= "Claim 8"
FT   Domain          167..186
FT                   /label= Transmembrane_domain
FT   Domain          187..294
FT                   /label= Cytoplasmic_domain
FT                   /note= "Claim 6"
FT   Peptide         34..71
FT                   /note= "TNFR_NGFR motif"
PN   WO9839361-A1.
PD   11-SEP-1998.
PF   03-MAR-1998; U04270.
PR   03-MAR-1997; US-810572.
PA   (SJUD-) ST JUDE CHILDREN'S RES HOSPITAL.
PI   Bram RJ, Von Bulow G;
DR   WPI; 98-506346/43.
DR   N-PSDB; V57328.
PT   New isolated transmembrane activator protein - used to develop
PT   products for treating e.g. infections, cancers, autoimmune and
PT   inflammatory conditions, transplant rejection or graft-versus-host
PT   disease
PS   Claim 20; Fig 2a; 89pp; English.
SQ   Sequence   293 AA;

  Query Match           100.0%;  Score 2210;  DB 36;  Length 293;
  Best Local Similarity 100.0%;  Pred. No. 6.58e-223;
  Matches   293;  Conservative    0;  Mismatches   0;  Indels   0;  Gaps   0;

Db      1 msglgrsrrggrsrvdqeerfpqglwtgvamrscpeeqywdpllgtcmsckticnhqsqr 60
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Qy      1 MSGLGRSRRGGRSRVDQEERFPQGLWTGVAMRSCPEEQYWDPLLGTCMSCKTICNHQSQR 60

Db     61 tcaafcrslscrkeqgkfydhllrdciscasicgqhpkqcayfcenklrspvnlppelrr 120
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Qy     61 TCAAFCRSLSCRKEQGKFYDHLLRDCISCASICGQHPKQCAYFCENKLRSPVNLPPELRR 120

Db    121 qrsgevennsdnsgryqglehrgseaspalpglklsadqvalvystlglclcavlccflv 180
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Qy    121 QRSGEVENNSDNSGRYQGLEHRGSEASPALPGLKLSADQVALVYSTLGLCLCAVLCCFLV 180

Db    181 avacflkkrgdpcscqprsrprqspakssqdhameagspvstspepvetcsfcfpecrap 240
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Qy    181 AVACFLKKRGDPCSCQPRSRPRQSPAKSSQDHAMEAGSPVSTSPEPVETCSFCFPECRAP 240

Db    241 tqesavtpgtpdptcagrwgchtrttvlqpcphipdsglgivcvpaqeggpga 293
          |||||||||||||||||||||||||||||||||||||||||||||||||||||
Qy    241 TQESAVTPGTPDPTCAGRWGCHTRTTVLQPCPHIPDSGLGIVCVPAQEGGPGA 293

Title:          >US-09-302-863-4
Description:    (1-285) from US09302863.pep
Perfect Score:  1998
Sequence:       1 MDDSTEREQSRLTSCLKKRE.....ENAQISLDGDVTFFGALKLL 285

Scoring table:  PAM 150
                Gap 11
```

```
Searched:         170751 seqs, 21266608 residues

Post-processing: Minimum Match 0%
                 Listing first 45 summaries

Database:        a-geneseq35
                                  SUMMARIES
                 %
Result           Query
   No.  Score    Match Length DB  ID          Description              Pred. No.
 ------------------------------------------------------------------------------
     3   1998  100.0    285 32  W58391      Homo sapiens neutroki  6.52e-172

                                 ALIGNMENTS

RESULT    3
ID   W58391 standard; Protein; 285 AA.
AC   W58391;
DT   11-SEP-1998  (first entry)
DE   Homo sapiens neutrokine alpha protein.
KW   neutrokine alpha; cell proliferation; differentiation; migration;
KW   cytotoxicity; cell death; treatment; tumour; infection; inflammation;
KW   wound healing; immunodeficiency; autoimmune disease; graft rejection;
KW   fibrotic disorder; haematopoiesis; sepsis; shock; malaria; HIV; AIDS;
KW   acquired immune deficiency syndrome; rheumatoid arthritis; silicosis;
KW   cachexia; detection; diagnosis; drug screening.
OS   Homo sapiens.
FH   Key             Location/Qualifiers
FT   Domain          1..46
FT                   /note= "intracellular domain"
FT   Domain          47..72
FT                   /note= "transmembrane domain"
FT   Domain          73..285
FT                   /note= "extracellular domain"
PN   WO9818921-A1.
PD   07-MAY-1998.
PF   25-OCT-1996; U17957.
PR   25-OCT-1996; WO-U17957.
PA   (HUMA-) HUMAN GENOME SCI INC.
PI   Ebner R, Ni J, Yu G;
DR   WPI; 98-272216/24.
DR   N-PSDB; V30934.
PT   New isolated human Neutrokine alpha - used to develop products for
PT   diagnosis and treatment of e.g. tumours, infections,
PT   immunodeficiencies or autoimmune diseases
PS   Claim 17; Fig 1; 104pp; English.
CC   The sequence is that of the neutrokine alpha protein.
CC   Neutrokine alpha (NA) polypeptides modulate cell proliferation,
CC   differentiation, migration, cytotoxicity and cell death.
CC   They can be used to treat e.g. tumour and tumour metastasis, infections
CC   by bacteria, viruses and other parasites, immunodeficiencies,
CC   inflammatory diseases, lymphadenopathy, autoimmune diseases, graft
CC   versus host disease and to stimulate peripheral tolerance, destroy some
CC   transformed cell lines, mediate cell activation and proliferation, and
CC   are functionally linked as primary mediators of immune regulation and
CC   inflammatory responses.  Such activity is useful for immune enhancement
CC   or suppression, myeloprotection, stem cell mobilisation, acute and
CC   chronic inflammatory control and treatment of leukaemia.  They can also
CC   be used to stimulate wound healing and to treat fibrotic disorders
CC   including liver cirrhosis, osteoarthritis and pulmonary fibrosis.  They
CC   can also be used to regulate haematopoiesis, by regulating the activation
CC   and differentiation of various haematopoietic progenitor cells, e.g. to
CC   release mature leukocytes from the bone marrow following chemotherapy,
CC   and in stem cell mobilisation.  NA may also be used to treat sepsis.  NA
CC   antagonists can be used to prevent septic shock, inflammation, cerebral
CC   malaria, activation of the HIV virus, graft-host rejection, bone
```

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CC   resorption, rheumatoid arthritis and cachexia (wasting or malnutrition).
CC   They can also be used to treat e.g. autoimmune diseases such as multiple
CC   sclerosis and insulin-dependent diabetes and inflammatory and infectious
CC   diseases such as silicosis, and sarcoidosis, idiopathic pulmonary
CC   fibrosis, idiopathic hyper-eosinophilic syndrome, endotoxic shock,
CC   atherosclerosis, histamine-mediated allergic reactions and immunological
CC   disorders including late phase allergic reactions, chronic urticaria, and
CC   atopic dermatitis by inhibiting chemokine-induced mast cell and basophil
CC   degranulation and release of histamine.  IgE-mediated allergic reactions
CC   such as allergic asthma, rhinitis and eczema, inflammatory pulmonary
CC   diseases, rheumatoid arthritis, inflammation, degenerative and
CC   inflammatory arthropathies, aplastic anaemia, myelodysplastic syndrome,
CC   subepithelial basement membrane fibrosis or adult respiratory distress
CC   syndrome. The products can also be used for detection, diagnosis and
CC   drug screening.
SQ   Sequence   285 AA;

  Query Match           100.0%;  Score 1998;  DB 32;  Length 285;
  Best Local Similarity 100.0%;  Pred. No. 6.52e-172;
  Matches   285;  Conservative    0;  Mismatches   0;  Indels   0;  Gaps   0;

Db      1 mddstereqsrltsclkkreemklkecvsilprkespsvrsskdgkllaatlllallscc 60
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Qy      1 MDDSTEREQSRLTSCLKKREEMKLKECVSILPRKESPSVRSSKDGKLLAATLLLALLSCC 60

Db     61 ltvvsfyqvaalqgdlaslraelqghhaeklpagagapkagleeapavtaglkifeppap 120
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Qy     61 LTVVSFYQVAALQGDLASLRAELQGHHAEKLPAGAGAPKAGLEEAPAVTAGLKIFEPPAP 120

Db    121 gegnssqnsrnkravqgpeetvtqdclqliadsetptiqkgsytfvpwllsfkrgsalee 180
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Qy    121 GEGNSSQNSRNKRAVQGPEETVTQDCLQLIADSETPTIQKGSYTFVPWLLSFKRGSALEE 180

Db    181 kenkilvketgyffiygqvlytdktyamghliqrkkvhvfgdelslvtlfrciqnmpetl 240
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Qy    181 KENKILVKETGYFFIYGQVLYTDKTYAMGHLIQRKKVHVFGDELSLVTLFRCIQNMPETL 240

Db    241 pnnscysagiakleegdelqlaiprenaqisldgdvtffgalkll 285
          |||||||||||||||||||||||||||||||||||||||||||||
Qy    241 PNNSCYSAGIAKLEEGDELQLAIPRENAQISLDGDVTFFGALKLL 285
```

Insofar as these amino acid sequences are identical, and insofar as Bram describes the universe of all nucleic acid molecules encoding TACI and Yu describes the universe of all nucleic acid molecules encoding neutrokine-α, then TACI is encoded by a nucleic acid molecule that is at lest 95% identical to SEQ ID NO: 1 and neutrokine-α is encoded by a nucleic acid molecule that is at least 95% identical to SEQ ID NO: 3.

TACI is also encoded by a nucleic acid molecule that is identical to SEQ ID NO: 1, and neutrokine-α is also encoded by a nucleic acid molecule that is identical to at least the coding sequence of SEQ ID NO: 3, as indicated below, respectively:

```
  Query Match           100.0%;  Score 1377;  DB 19;  Length 1377;
  Best Local Similarity 100.0%;  Pred. No. 0;
```

```
  Matches 1377;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy      1 agcatcctgagtaatgagtggcctgggccggagcaggcgaggtggccggagccgtgtgga 60
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      1 agcatcctgagtaatgagtggcctgggccggagcaggcgaggtggccggagccgtgtgga 60

Qy     61 ccaggaggagcgctttccacagggcctgtggacgggggtggctatgagatcctgccccga 120
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     61 ccaggaggagcgctttccacagggcctgtggacgggggtggctatgagatcctgccccga 120

Qy    121 agagcagtactgggatcctctgctgggtacctgcatgtcctgcaaaaccatttgcaacca 180
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    121 agagcagtactgggatcctctgctgggtacctgcatgtcctgcaaaaccatttgcaacca 180

Qy    181 tcagagccagcgcacctgtgcagccttctgcaggtcactcagctgccgcaaggagcaagg 240
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    181 tcagagccagcgcacctgtgcagccttctgcaggtcactcagctgccgcaaggagcaagg 240

Qy    241 caagttctatgaccatctcctgagggactgcatcagctgtgcctccatctgtggacagca 300
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    241 caagttctatgaccatctcctgagggactgcatcagctgtgcctccatctgtggacagca 300

Qy    301 ccctaagcaatgtgcatacttctgtgagaacaagctcaggagcccagtgaaccttccacc 360
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    301 ccctaagcaatgtgcatacttctgtgagaacaagctcaggagcccagtgaaccttccacc 360

Qy    361 agagctcaggagacagcggagtggagaagttgaaaacaattcagacaactcgggaaggta 420
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    361 agagctcaggagacagcggagtggagaagttgaaaacaattcagacaactcgggaaggta 420

Qy    421 ccaaggattggagcacagaggctcagaagcaagtccagctctcccggggctgaagctgag 480
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    421 ccaaggattggagcacagaggctcagaagcaagtccagctctcccggggctgaagctgag 480

Qy    481 tgcagatcaggtggccctggtctacagcacgctggggctctgcctgtgtgccgtcctctg 540
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    481 tgcagatcaggtggccctggtctacagcacgctggggctctgcctgtgtgccgtcctctg 540

Qy    541 ctgcttcctggtggcggtggcctgcttcctcaagaagagggggggatccctgctcctgcca 600
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    541 ctgcttcctggtggcggtggcctgcttcctcaagaagagggggggatccctgctcctgcca 600

Qy    601 gccccgctcaaggccccgtcaaagtccggccaagtcttcccaggatcacgcgatggaagc 660
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    601 gccccgctcaaggccccgtcaaagtccggccaagtcttcccaggatcacgcgatggaagc 660

Qy    661 cggcagccctgtgagcacatcccccgagccagtggagacctgcagcttctgcttccctga 720
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    661 cggcagccctgtgagcacatcccccgagccagtggagacctgcagcttctgcttccctga 720

Qy    721 gtgcagggcgcccacgcaggagagcgcagtcacgcctgggacccccgaccccacttgtgc 780
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    721 gtgcagggcgcccacgcaggagagcgcagtcacgcctgggacccccgaccccacttgtgc 780

Qy    781 tggaaggtgggggtgccacaccaggaccacagtcctgcagccttgcccacacatcccaga 840
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    781 tggaaggtgggggtgccacaccaggaccacagtcctgcagccttgcccacacatcccaga 840

Qy    841 cagtggccttggcattgtgtgtgtgcctgcccaggaggggggcccaggtgcataaatggg 900
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    841 cagtggccttggcattgtgtgtgtgcctgcccaggaggggggcccaggtgcataaatggg 900

Qy    901 ggtcagggagggaaaggaggagggagagagatggagaggaggggagagagaaagagaggt 960
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    901 ggtcagggagggaaaggaggagggagagagatggagaggaggggagagagaaagagaggt 960

Qy    961 ggggagaggggagagagatatgaggagagagagacagaggaggcagaaagggagagaaac 1020
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```
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     961 ggggagaggggagagagatatgaggagagagagacagaggaggcagaaagggagagaaac 1020

Qy    1021 agaggagacagagagggagagagagacagagggagagagagacagaggggaagagaggca 1080
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    1021 agaggagacagagagggagagagagacagagggagagagagacagaggggaagagaggca 1080

Qy    1081 gagagggaaagaggcagagaaggaaagagacaggcagagaaggagagaggcagagaggga 1140
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    1081 gagagggaaagaggcagagaaggaaagagacaggcagagaaggagagaggcagagaggga 1140

Qy    1141 gagaggcagagagggagagaggcagagagacagagagggagagagggacagagagagata 1200
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    1141 gagaggcagagagggagagaggcagagagacagagagggagagagggacagagagagata 1200

Qy    1201 gagcaggaggtcggggcactctgagtcccagttcccagtgcagctgtaggtcgtcatcac 1260
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    1201 gagcaggaggtcggggcactctgagtcccagttcccagtgcagctgtaggtcgtcatcac 1260

Qy    1261 ctaaccacacgtgcaataaagtcctcgtgcctgctgctcacagcccccgagagcccctcc 1320
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    1261 ctaaccacacgtgcaataaagtcctcgtgcctgctgctcacagcccccgagagcccctcc 1320

Qy    1321 tcctggagaataaaaccttggcagctgcccttcctcaaaaaaaaaaaaaaaaaaaa 1377
                |||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    1321 tcctggagaataaaaccttggcagctgcccttcctcaaaaaaaaaaaaaaaaaaaa 1377
```

```
  Query Match             92.1%;  Score 973;  DB 19;  Length 1100;
  Best Local Similarity   100.0%;  Pred. No. 1.9e-231;
  Matches  973;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy      39 tcaaagttcaagtagtgatatggatgactccacagaaagggagcagtcacgccttacttc 98
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     128 tcaaagttcaagtagtgatatggatgactccacagaaagggagcagtcacgccttacttc 187

Qy      99 ttgccttaagaaaagagaagaaatgaaactgaaggagtgtgtttccatcctcccacggaa 158
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     188 ttgccttaagaaaagagaagaaatgaaactgaaggagtgtgtttccatcctcccacggaa 247

Qy     159 ggaaagcccctctgtccgatcctccaaagacggaaagctgctggctgcaaccttgctgct 218
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     248 ggaaagcccctctgtccgatcctccaaagacggaaagctgctggctgcaaccttgctgct 307

Qy     219 ggcactgctgtcttgctgcctcacggtggtgtctttctaccaggtggccgccctgcaagg 278
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     308 ggcactgctgtcttgctgcctcacggtggtgtctttctaccaggtggccgccctgcaagg 367

Qy     279 ggacctggccagcctccgggcagagctgcagggccaccacgcggagaagctgccagcagg 338
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     368 ggacctggccagcctccgggcagagctgcagggccaccacgcggagaagctgccagcagg 427

Qy     339 agcaggagcccccaaggccggcctggaggaagctccagctgtcaccgcgggactgaaaat 398
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     428 agcaggagcccccaaggccggcctggaggaagctccagctgtcaccgcgggactgaaaat 487

Qy     399 ctttgaaccaccagctccaggagaaggcaactccagtcagaacagcagaaataagcgtgc 458
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     488 ctttgaaccaccagctccaggagaaggcaactccagtcagaacagcagaaataagcgtgc 547

Qy     459 cgttcagggtccagaagaaacagtcactcaagactgcttgcaactgattgcagacagtga 518
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     548 cgttcagggtccagaagaaacagtcactcaagactgcttgcaactgattgcagacagtga 607

Qy     519 aacaccaactatacaaaaaggatcttacacatttgttccatggcttctcagctttaaaag 578
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Db    608 aacaccaactatacaaaaaggatcttacacatttgttccatggcttctcagctttaaaag 667

Qy    579 gggaagtgccctagaagaaaaagagaataaaatattggtcaaagaaactggttacttttt 638
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    668 gggaagtgccctagaagaaaaagagaataaaatattggtcaaagaaactggttacttttt 727

Qy    639 tatatatggtcaggttttatatactgataagacctacgccatgggacatctaattcagag 698
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    728 tatatatggtcaggttttatatactgataagacctacgccatgggacatctaattcagag 787

Qy    699 gaagaaggtccatgtctttggggatgaattgagtctggtgactttgtttcgatgtattca 758
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    788 gaagaaggtccatgtctttggggatgaattgagtctggtgactttgtttcgatgtattca 847

Qy    759 aaatatgcctgaaacactacccaataattcctgctattcagctggcattgcaaaactgga 818
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    848 aaatatgcctgaaacactacccaataattcctgctattcagctggcattgcaaaactgga 907

Qy    819 agaaggagatgaactccaacttgcaataccaagagaaaatgcacaaatatcactggatgg 878
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    908 agaaggagatgaactccaacttgcaataccaagagaaaatgcacaaatatcactggatgg 967

Qy    879 agatgtcacatttttttggtgcattgaaactgctgtgacctacttacaccatgtctgtagc 938
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    968 agatgtcacatttttttggtgcattgaaactgctgtgacctacttacaccatgtctgtagc 1027

Qy    939 tattttcctccctttctctgtacctctaagaagaaagaatctaactgaaaataccaaaaa 998
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db   1028 tattttcctccctttctctgtacctctaagaagaaagaatctaactgaaaataccaaaaa 1087

Qy    999 aaaaaaaaaaaaa 1011
          |||||||||||||
Db   1088 aaaaaaaaaaaaa 1100
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Regarding TACI and screening methods for agonist and antagonist thereto, Bram discloses:

The receptor protein can be used to identify ligands of the protein receptor. The soluble, extracellular domain can be used to inhibit cellular activation. The protein may also be used for diagnostic purposes and for identifying agents for modulating the calcium induced activation pathway. Page 3, last full paragraph.

Either activating or inhibiting the function of the novel cell surface receptor of the present invention can be used to treat cancers of T and B cells. Page 4, full paragraph 1.

The antibodies of the present invention can be either monoclonal antibodies or polyclonal antibodies. In one embodiment, the antibody is a monoclonal antibody that is a chimeric antibody. Page 9, full paragraph 1.

When activated, the TACI protein stimulates the influx of calcium in lymphocytes. Page 15, full paragraph 1.

In general, there is substantial interest in identifying specific components of cellular pathways to allow for understanding an activation pathway, selectively modulating that pathway, and developing drugs which may be active

in binding to the target protein. In this way, drugs can be screened to inhibit such specific pathways. Page 17, full paragraph 2.

Cross-linking the TACI protein activates calcium influx (page 18, full paragraph 1). The extracellular domain binds ligand. Upon ligand binding, the cytoplasmic domain binds CAML, thus initiating a Ca^{2+} -dependent activation pathway. Page 18, full paragraph 2.

A chimeric TACI protein of the invention may be a protein that is generated by joining a functional domain of a TACI protein, such as the ligand binding domain or the CAML-binding domain, with the complementary domain of another protein, e.g., an alternative receptor. Chimeric constructs can also be prepared with a functionally active fragment of a TACI protein and another functionally active molecule. For example, the extracellular domain of a TACI protein may be joined to the Fc domain of an immunoglobulin. Page 24, line 20 through page 25, line 21.

Monovalent antibody reagents can act to block access to TACI in lymphocytes (page 49, last full paragraph). Such antibodies include but are not limited to polyclonal, monoclonal, chimeric, single chain, Fab fragments, and an Fab expression library (paragraph bridging pages 49-50). Such human or humanized chimeric antibodies are preferred for use in therapy of human diseases or disorders, since the human or humanized antibodies are much less likely than xenogeneic antibodies to induce an immune response, in particular an allergic response, themselves (paragraph bridging pages 50-51). Such fragments include but are not limited to the $F(ab')_2$ fragment (page 51, full paragraph 2).

The TACI protein can be used, to screen clones in order to identify the endogenous ligand(s). This ligand is likely to be involved in the regulation of the immune system as well, and thus should have similar or complementary uses to those described herein. Page 52, last full paragraph.

Any screening technique known in the art can be used to screen for TACI protein agonists or antagonists. The present invention contemplates screens for small molecule ligands or ligand analogs and mimics, as well as screens for the natural ligand(s) that bind to and agonize or antagonize the TACI protein in vivo. For example, natural products libraries can be screened using assays of the invention for molecules that agonize or antagonize the TACI protein activity, or that bind to the extracellular domain or cytoplasmic domain of TACI. Page 53, full paragraph 1.

Alternatively, assays for binding of soluble ligand to cells that express recombinant forms of the TACI N-Terminal extracellular domain can be performed. The soluble ligands can be provided readily as recombinant or synthetic polypeptides. The screening can be performed with recombinant cells that express TACI, or a fragment thereof, or alternatively, using purified protein, e.g., produced recombinantly, as described above. For example, the ability of labeled, soluble or solubilized TACI fragment to bind ligand can be used to screen libraries, as described in the foregoing references. Page 54, full paragraphs 1-2.

Regarding neutrokine-α and screening methods for agonist and antagonist thereto, Yu discloses:

> In another aspect, a method for identifying Neutrokine-α receptors is provided, as well as a screening assay for agonists and antagonists using such receptors. This assay involves determining the effect a candidate compound has on Neutrokine-α binding to the Neutrokine-α receptor. In particular, the method involves contacting a Neutrokine-α receptor with a Neutrokine-α polypeptide and a candidate compound and determining whether Neutrokine-α polypeptide binding to the Neutrokine-α receptor is increased or decreased due to the presence of the candidate compound. The antagonists may be employed to prevent septic shock, inflammation, cerebral malaria, activation of the HIV virus, graft-host rejection, bone resorption, rheumatoid arthritis and cachexia (wasting or malnutrition) (page 12, full paragraph 1).
>
> In the assay of the invention for agonists or antagonists, a cellular compartment, such as a membrane or a preparation thereof, may be prepared from a cell that expresses a molecule that binds Neutrokine-α such as a molecule of a signaling or regulatory pathway modulated by Neutrokine-α. The preparation is incubated with labeled Neutrokine-α in the absence or the presence of a candidate molecule which may be a Neutrokine-α agonist or antagonist. The ability of the candidate molecule to bind the binding molecule is reflected in decreased binding of the labeled ligand. Molecules which bind gratuitously, i.e., without inducing the effects of Neutrokine-α on binding the Neutrokine-α binding molecule, are most likely to be good antagonists. Molecules that bind well and elicit effects that are the same as or closely related to Neutrokine-α are agonists.
>
> Neutrokine-α-like effects of potential agonists and antagonists may by measured, for instance, by determining activity of a second messenger system following interaction of the candidate molecule with a cell or appropriate cell preparation, and comparing the effect with that of Neutrokine-α or molecules that elicit the same effects as Neutrokine-α. Second messenger systems that may be useful in this regard include but are not limited to AMP guanylate cyclase, ion channel or phosphoinositide hydrolysis second messenger systems. Page 55, full paragraph 1.
>
> Another example of an assay for Neutrokine-α antagonists is a competitive assay that combines Neutrokine-α and a potential antagonist with membrane-bound receptor molecules or recombinant Neutrokine-α receptor molecules under appropriate conditions for a competitive inhibition assay. Neutrokine-α can be labeled, such as by radioactivity, such that the number of Neutrokine-α molecules bound to a receptor molecule can be determined accurately to assess the effectiveness of the potential antagonist. Page 55, full paragraph 2.
>
> Potential antagonists include small organic molecules, peptides, polypeptides and antibodies that bind to a polypeptide of the invention and thereby inhibit or extinguish its activity. Potential antagonists also may be small organic molecules, a peptide, a polypeptide such as a closely related protein or antibody that binds the same sites on a binding molecule, such as a receptor molecule, without inducing Neutrokine-α induced activities, thereby

preventing the action of Neutrokine-α by excluding Neutrokine-α from binding. Page 55, full paragraph 3

Antibodies against Neutrokine-α may be employed to bind to and inhibit Neutrokine-α activity. Page 57, last full paragraph.

Neutrokine-α polypeptides can be combined with parts of the constant domain of immunoglobulins (IgG), resulting in chimeric polypeptides. These fusion proteins facilitate purification and show an increased half-life in vivo. Fusion proteins that have a disulfide-linked dimeric structure due to the IgG part can also be more efficient in binding and neutralizing other molecules than the monomeric Neutrokine-α protein or protein fragment alone. Paragraph bridging pages 41-42.

The term "antibody" (Ab) or "monoclonal antibody" (mAb) is meant to include intact molecules as well as fragments thereof (such as, for example, Fab and $F(ab')_2$ fragments) which are capable of binding an antigen. Fab, $F(ab')_2$ and F(ab') fragments lack the Fc fragment intact antibody, clear more rapidly from the circulation, and may have less non-specific tissue binding of an intact antibody. Page 46, full paragraph 1.

Bram and Yu do not teach that TACI and neutrokine-α bind.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to form a composition comprising (1) TACI, or fragment thereof that binds neutrokine-α, (2) neutrokine-α, or a fragment thereof that binds TACI, and (3) a test compound, assay for the level of interaction of TACI with neutrokine-α, and identify a test compound that affects the interaction with TACI and neutrokine-α, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification in order to regulate the activity of B cells.

It would have been further obvious to one of ordinary skill in the art at the time of Applicants' invention to label the neutrokine-α, such as by radioactivity, with a reasonable expectation of success, such that the number of neutrokine-α molecules bound to TACI can be determined accurately to assess the effectiveness of the potential antagonist or agonist.

It would have been further obvious to one of ordinary skill in the art at the time of Applicants' invention to identify a human or humanized antibody that affects the interaction of TACI and neutrokine-α, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because human or humanized antibodies are preferred for use in therapy of human diseases or disorders, since the human or humanized antibodies are much less likely than xenogeneic antibodies to induce an immune response, in particular an allergic response, themselves. Such human or humanized antibodies comprise a Fab fragment or a $F(ab')_2$ fragment.

Selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results. Selection of any order of mixing ingredients is prima facie obvious.

It would have been further obvious to one of ordinary skill in the art at the time of Applicants' invention to form a composition comprising TACI, neutrokine-α, and a test compound, assay for the level of interaction of TACI with neutrokine-α, and identify a test compound that affects the interaction with TACI and neutrokine-α, wherein the neutrokine-α further comprises a Fc domain, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make his modification because fusion proteins that have a disulfide-linked dimeric structure due to the IgG part can also be more efficient in binding and neutralizing other molecules than the monomeric Neutrokine-α protein or protein fragment alone.

It would have been further obvious to one of ordinary skill in the art at the time of Applicants' invention to form a composition comprising TACI, neutrokine-α, and a test

compound, assay for the level of interaction of TACI with neutrokine-α, and identify a test compound that affects the interaction with TACI and neutrokine-α, wherein the TACI further comprises a Fc domain, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make his modification because it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention that the soluble, extracellular domain of TACI can be used to inhibit cellular activation by biding neutrokine-α and fusion proteins that have a dimeric structure can also be more efficient in binding and neutralizing other molecules than the monomeric TACI or TACI fragment alone.

It would have been further obvious to one of ordinary skill in the art at the time of Applicants' invention assess the activation of TACI in a cell as measured by calcium influx because neutrokine-α-like effects of potential agonists and antagonists may by measured, for instance, by determining activity of a second messenger system following interaction of the candidate molecule with a cell or appropriate cell preparation, and when activated, the TACI protein stimulates the influx of calcium in lymphocytes.

The invention is prima facie obvious over the prior art.

Claims 15 and 25–26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gross in view of Bram and Yu as applied to claims 15, 25, and 35 above, and further in view of Nocka (U. S. Patent No. 5,525,708).

Gross in view of Bram and Yu teach forming a composition comprising TACI, neutrokine-α, and a test compound, assaying for the level of interaction of TACI with neutrokine-α, and identifying a test compound that affects the interaction with TACI and

neutrokine-α, wherein the neutrokine-α further comprises a Fc domain, as discussed above. Gross in view of Bram and Yu do not teach forming a composition comprising TACI, neutrokine-α, and a test compound, assaying for the level of interaction of TACI with neutrokine-α, and identifying a test compound that affects the interaction with TACI and neutrokine-α, wherein the neutrokine-α further comprises a leucine zipper domain.

Stabilized dimers with increased biological activity can also be produced through non-covalent means by the fusion with domains that readily form stable hetero- or homomeric multimers. An example would be to use the so called "Leucine zipper" domain which will self associate with another protein that contains a Leucine zipper domain. See Nocka column 7, lines 42-47. Nocka does not teach forming a composition comprising TACI, neutrokine-α, and a test compound, assaying for the level of interaction of TACI with neutrokine-α, and identifying a test compound that affects the interaction with TACI and neutrokine-α, wherein the neutrokine-α further comprises a leucine zipper domain.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to form a composition comprising TACI, neutrokine-α, and a test compound, assay for the level of interaction of TACI with neutrokine-α, and identify a test compound that affects the interaction with TACI and neutrokine-α, wherein the neutrokine-α further comprises a Fc domain, as taught by Gross in view of Bram and Yu, and to modify that teaching by substituting a leucine zipper domain, as taught by Nocka, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this combination because stabilized dimers with increased biological activity can also be produced through non-covalent means by the fusion with domains that readily form stable hetero- or

homomeric multimers, such as the so called "Leucine zipper" domain, which will self associate with another protein that contains a Leucine zipper domain.

The invention is prima facie obvious over the prior art.

Claims 15 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gross in view of Bram and Yu as applied to claim 15 above, and further in view of Creighton.

Gross in view of Bram and Yu teach forming a composition comprising TACI, neutrokine-α, and a test compound, assaying for the level of interaction of TACI with neutrokine-α, and identifying a test compound that affects the interaction with TACI and neutrokine-α, wherein the TACI, neutrokine-α, and test compound are combined under appropriate conditions for a competitive inhibition assay, as discussed above. Gross in view of Bram and Yu do not expressly teach forming a composition comprising TACI, neutrokine-α, and a test compound, assaying for the level of interaction of TACI with neutrokine-α, and identifying a test compound that affects the interaction with TACI and neutrokine-α, wherein the TACI, neutrokine-α, and test compound are combined under appropriate conditions for a competitive inhibition assay, wherein the competitive inhibition assay comprises determining a dissociation constant of the interaction of TACI and neutrokine-α.

A competitive inhibition assay, as taught by Yu, implies or suggest determining a dissociation constant because the specificity of protein-ligand binding is determined by their relative affinities. The affinity between a protein and a ligand is measured by the association constant, K_a. However, the value of K_a has units of (concentration)$^{-1}$, and it is often intuitively easier to consider the dissociation constant, K_d, which is the reciprocal of K_a. See Creighton,

pages 336-337. Creighton does not teach forming a composition comprising TACI, neutrokine-α, and a test compound, assaying for the level of interaction of TACI with neutrokine-α, and identifying a test compound that affects the interaction with TACI and neutrokine-α, wherein the TACI, neutrokine-α, and test compound are combined under appropriate conditions for a competitive inhibition assay.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to form a composition comprising TACI, neutrokine-α, and a test compound, assay for the level of interaction of TACI with neutrokine-α, and identify a test compound that affects the interaction with TACI and neutrokine-α, wherein the TACI, neutrokine-α, and test compound are combined under appropriate conditions for a competitive inhibition assay, as taught by Gross in view of Bram and Yu, and to modify that teaching by determining a dissociation constant, as taught by Creighton, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this competition because it is often intuitively easier to consider the dissociation constant, K_d, which is the reciprocal of K_a. The invention is prima facie obvious over the prior art.

Claims 15 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gross in view of Bram and Yu as applied to claim 15 above, and further in view of Alberts (1983) and Hu (U. S. Patent No. 5,932,540).

Gross in view of Bram and Yu teach a method of identifying a test compound that affects the interaction with TACI and neutrokine-α, as discussed above. Gross in view of Bram and Yu

do not expressly teach a method of identifying a test compound that affects the interaction with TACI and neutrokine-α wherein both TACI and neutrokine-α are soluble.

Alberts discloses that when the detergent is removed, solubilized membrane proteins usually become highly insoluble and precipitate (paragraph bridging pages 265-266). The naked membrane protein molecules tend to bury their hydrophobic regions by clustering together, forming large aggregates that precipitate from solution (page 266, Figure 6–19).

The prevention of aggregation is highly desirable. Aggregation of proteins results in a loss of activity. See Hu, column 11, full paragraph 3.

Alberts and Hu do not teach a method of identifying a test compound that affects the interaction with TACI and neutrokine-α wherein both TACI and neutrokine-α are soluble.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention identify a test compound that affects the interaction with TACI and neutrokine-α, as taught by Gross in view of Bram and Yu, and to modify that teaching by making soluble fragments of TACI and neutrokine-α, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because aggregation results in a loss of activity.

The invention is prima facie obvious over the prior art.

Claims 15 and 17–18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gross in view of Bram and Yu and further in view of Alberts (1983) and Hu (U. S. Patent No. 5,932,540) as applied to claims 15 and 17 above and further in view of Ullman (U. S. Patent No. 5,340,716).

Gross in view of Bram and Yu and further in view of Alberts and Hu teach a method of identifying a test compound that affects the interaction with TACI and neutrokine-α, wherein both TACI and neutrokine-α are soluble, as discussed above. Gross in view of Bram and Yu and further in view of Alberts and Hu do not teach a method of identifying a test compound that affects the interaction with TACI and neutrokine-α wherein both TACI and neutrokine-α are soluble, wherein both TACI and neutrokine-α are labeled.

Ullman teaches that in a receptor-ligand binding assay both the receptor and ligand can be labeled with different labels where the labels interact when in close proximity and the amount of ligand present affects the degree to which the labels interact (column 1, lines 45-49). Ullman does not teach a method of identifying a test compound that affects the interaction with TACI and neutrokine-α wherein both TACI and neutrokine-α are soluble.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to identify a test compound that affects the interaction with TACI and neutrokine-α, wherein both TACI and neutrokine-α are soluble, as taught by Gross in view of Bram and Yu and further in view of Alberts and Hu, and to modify that teaching by labeling both TACI and neutrokine-α with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because any screening technique known in the art can be used to screen for TACI protein agonists or antagonists and it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention that when both the receptor and ligand are labeled with different labels wherein the labels interact when in close proximity that the amount of label interaction would be a measure of the degree to which a potential agonists or antagonists affects the interaction of TACI with neutrokine-α.

The invention is prima facie obvious over the prior art.

Conclusion

No claims are allowable.

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DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
AUGUST 6, 2006